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Long-term treatment of chronic migraine with OnabotulinumtoxinA: efficacy, quality of life and tolerability in a real-life setting

Katja Kollewe[1] · Claus M. Escher[1] · Dirk U. Wulff[2] · Davood Fathi[1,3,4] · Lejla Paracka[1] · Bahram Mohammadi[4,5] · Matthias Karst[6] · Dirk Dressler[1]

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Abstract Botulinum toxin was shown to be effective in treatment of chronic migraine. We wanted to explore its efficacy and tolerability in chronic application under real-life conditions. For this, 27 consecutive patients (age 45.6 ± 10.8 years, 25 females, 2 males) received altogether 176 injection series (IS) with 189.7 ± 45.8MU onabotulinumtoxinA (Botox®) according to the PREEMPT scheme. During the study period altogether 6.5 ± 2.9 (min 4, max 13) IS were applied per patient (total treatment time of 73.1 ± 36.9 weeks). 96 % of the patients reported benefit. Monthly headache days were reduced from 18.9 ± 3.9 to 8.7 ± 4.5 ($p < 0.001$, −53.7 %), migraine days from 16.8 ± 4.9 to 7.4 ± 4.6 ($p < 0.001$, −55.1 %), autonomic days from 8.6 ± 7.5 to 2.7 ± 4.2 ($p < 0.001$, −71.9 %) and medication days from 14.2 ± 4.6 to 8.3 ± 4.2 ($p < 0.001$, −71.1 %). Health-related quality of life improved by 0.6–1.5 standard deviations (SD) (Short Form Health Survey), migraine-related quality of life by 1.4–2.0 SD (Migraine-Specific Quality of Life Questionnaire) and by 1.9 SD (Headache Impact Test), depression by 1.1 SD (Beck Depression Inventory). Subjective global clinical improvement was 2.6 ± 0.6 (Global Clinical Improvement Scale). All improvements were stable throughout the entire study period. Adverse effects were infrequent, mild and transient. Botulinum toxin provides highly effective and safe long-term treatment of chronic migraine.

Keywords Botulinum toxin · Botox® · OnabotulinumtoxinA · Chronic migraine · Long-term treatment · Real-life setting

Introduction

Migraine is a neurological condition characterized by episodes of severe pulsating unilateral headache. It is frequently associated with nausea, photophobia and phonophobia and often aggravated by physical activity. It may be divided into Episodic Migraine (EM) with less than 15 and Chronic Migraine (CM) with more than 15 headache days per month for 3 months with typical features of migraine on at least 8 days (Headache Classification Committee of the International Headache S 2013). CM has an estimated prevalence of about 2 %, ranging from 0.2 to 5.1 % in international studies (Manack et al. 2011; Natoli et al. 2010). Women are much more frequently affected than men with a female–male ratio of 6.5:1.0 (Castillo et al. 1999). For both, genders prevalence peaks between 18 and 49 years of age (Buse et al. 2012). CM produces an enormous burden of disease illustrated by the following observations: CM patients are missing at work, show

K. Kollewe and C. M. Escher contributed equally.

✉ Katja Kollewe
kollewe.katja@mh-hannover.de

1 Department of Neurology, Movement Disorder Section, Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover, Germany

2 Max Planck Institute for Human Development, Berlin, Germany

3 Brain and Spinal Injury Research Center, Tehran University of Medical Sciences, Tehran, Iran

4 International Neuroscience Institute, Hannover, Germany

5 Department of Neurology, University of Lübeck, Lübeck, Germany

6 Department of Anaesthesiology, Pain Clinic, Hannover Medical School, Hannover, Germany

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reduced household productivity (Bigal et al. 2008), are less likely to be employed full-time, have lower incomes and may be occupationally disabled (Buse et al. 2010). CM patients also have an increased risk for comorbidities such as depression, stroke, chronic obstructive pulmonary disease, asthma bronchiale (Katsarava et al. 2012) and medication overuse (Bigal et al. 2004). They require more primary care visits, specialist visits, emergency room visits and are hospitalized more often (Blumenfeld et al. 2011) all together amounting to a substantial loss of quality of life (Blumenfeld et al. 2011; Guitera et al. 2002).

Treatment of migraine can be acute and prophylactic. Acute treatment is basically identical in CM and EM. However, it is important to restrict intake of migraine aborting drugs to 10 days per month to avoid Medication Overuse Headache (Headache Classification Committee of the International Headache S 2013). Prophylactic treatment includes substances such as metoprolol, propranolol, flunarizine, valproate and topiramate.

Long-term treatment of CM should include treatment of comorbidities, non-pharmacological prophylaxis (e.g. physical exercise, behavioral therapy, biofeedback treatment, progressive muscle relaxation) (Diener and Weimar 2012), avoidance of migraine triggers and modification of risk factors including losing weight, avoiding caffeine, alcohol and stress and getting sufficient sleep (Schwedt 2014).

However, both, acute and prophylactic treatment of migraine may produce adverse effects. In acute migraine treatment abortive migraine attacks remain. Search for new effective and safe migraine drugs, therefore, remains a challenge.

Positive effects of onabotulinumtoxinA on migraine was first noticed in patients receiving treatment for blepharospasm (Dressler, personal observations) and hyperfunctional facial lines (Binder et al. 2000). However, several subsequent studies failed to demonstrate positive effects on migraine and tension headaches (Evers et al. 2002; Jackson et al. 2012; Petri et al. 2009; Rollnik et al. 2000; Silberstein et al. 2000). Eventually, two multicenter, randomized, placebo-controlled clinical trials conducted by the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) study group demonstrated positive effects on the number of headache days and migraine days in CM patients (Aurora et al. 2010). This effect was confirmed as a primary endpoint in the second trial (Diener et al. 2010). Pooled data from both trials show that treatment is safe, well tolerated (Aurora et al. 2014) and increases quality of life (Lipton et al. 2011). With these positive results onabotulinumtoxinA was approved for treatment of CM in September 2011 by the Federal Institute for Drugs and Medical Devices (FDA) and subsequently many other registration authorities world-wide. In Germany the Bundesinstitut für Arzneimittel und Medizinprodukte (BfARM) approved onabotulinumtoxinA for treatment of CM in patients unresponsive to conventional treatment. Guidelines of the Deutsche Gesellschaft für Neurologie (DGN) recommend onabotulinumtoxinA as effective in the prophylactic treatment of CM with or without medication overuse. It should, however, only be used by physicians experienced in diagnosis and treatment of CM (Diener and Weimar 2012).

Methods

Study design The study design was based on a prospective observational design approved by the local ethical committee. Written consent was obtained from every patient entering the study. The observation period started 4 weeks before the first BT injection series (IS) was applied and ended 8 weeks after the fourth IS. Altogether four treatment cycles were recorded each lasting approximately 12 weeks. Throughout the observation period patients were asked to keep a headache diary. Assessment of health-related quality of life, migraine-related quality of life and depression was carried out before the first IS and 6 weeks after each of the four subsequent IS. The extension period included all treatment cycles after the observation period. Throughout the observation and the extension period BT therapy parameters including global clinical improvement, single BT dose, latency and duration of effect, as well as adverse effects were monitored.

Patients Between January 2012 and March 2014 altogether 27 consecutive patients with CM were enrolled. All patients were diagnosed with CM according to International Headache Society criteria and had received prophylactic treatment with at least one substance in the past with either insufficient effect or intolerable adverse effects. From all patients a medical history, a complete neurologic examination and magnetic resonance imaging (MRI) were obtained.

Botulinum toxin therapy For comparison reasons BT therapy was performed according to the PREEMPT injection scheme: 200 MU of onabotulinumtoxinA were diluted with 5 ml 0.9 % NaCl/H_20 yielding a concentration of 40 MU/ml. In the initial IS a total of 155 MU were applied to the M. corrugator (5 MU), M. procerus (5 MU), M. frontalis (10 MU), M. temporalis (20 MU), M. occipitalis (15 MU), cervical paraspinal muscles (10 MU) and M. trapezius (15 MU) on one side of the head (Blumenfeld et al. 2010). In subsequent IS up to 40 MU could be additionally administered into the M. trapezius (10 MU), M. occipitalis (5 MU) and M.

temporalis (5 MU) if patients reported additional painful spots or unilateral accentuation of pain by a follow the pain (FTP) strategy. In this case the maximum BT dose was 195 MU.

Botulinum toxin therapy parameters For every treatment cycle during the observation and the extension period the total BT dose applied as well as the target muscles selected together with their individual BT doses were recorded. BT's therapeutic effect was described by its latency (time between BT application and first signs of therapeutic effects, given in days) and its duration (time between BT application and first signs of wearing off of the therapeutic effect, given in weeks).

Efficacy parameters With the headache diary the patient documented headache days (days with more than 4 h of headache irrespective of pain quality and associated symptoms), migraine days (days with typical features of migraine), autonomic days (days with migraine and nausea or vomiting), medication days (days with intake of acute pain medication) and adverse effects.

Global clinical improvement compared to pre-treatment status was rated by the patient with the Global Clinical Improvement Scale (GCI). The GCI gives a general rating of the therapeutic effect and consists of a 4-point scale (0 = no, 1 = slight, 2 = moderate, 3 = marked improvement in severity and function). It resembles scales described elsewhere (Kollewe et al. 2010, 2015; Mohammadi et al. 2009; Rollnik et al. 2000). Health-related quality of life was documented by the patient with the Short Form Health Survey (SF-36). It consists of eight scaled scores: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health. The raw scores are transformed into scale scores from 0 to 100, higher scale scores refer to better health related quality of life.

Migraine-related quality of life was assessed by the patient on the Migraine-Specific Quality of Life Questionnaire (MSQ), which evaluates the impact of migraine on quality of life during the past 4 weeks (Jhingran et al. 1998). It is divided in three domains: role function restrictive, role function preventive and emotional function. It has been validated for CM (Bagley et al. 2012). Item scores are transformed into scale scores ranging from 0 to 100. Higher scale scores reflect a better migraine-related quality of life. Migraine-related quality of life was also assessed by the patient with the Headache Impact Test (HIT-6) originally designed to provide a global measure of adverse headache impact (Kosinski et al. 2003). It has been specifically validated for CM (Yang et al. 2011). Its six items are summed up to scores from 36 to 78, lower scores mean better migraine-related quality of life, a total score above 60 indicates a severe impact on migraine-related quality of life.

Depression was evaluated with the Beck Depression Inventory (BDI) a validated 21-item screening test for depression (Kühner et al. 2007). It is also one of the most widely used instruments for measuring depression severity. Each item is scored with a value from 0 to 3. Item scores are then summed up. It differentiates between no/minimal depression ($\leq$13), mild depression (14–19), moderate depression (20–28) and severe depression ($\geq$29).

Statistical analysis Statistical analysis of our data was conducted with the Statistical Package for the Social Sciences (SPSS, Version 19, IBM, Ehningen, Germany). All averages are given in mean $\pm$ standard deviation (SD). Headache diary data from the pre-treatment time were compared with diary data from week 4 to week 8 after each IS as there is a latency of effect in the first 2 weeks and a decline of effect after approximately 10 weeks. Data from SF-36, MSQ, HIT-6 and BDI before the initial treatment were compared with data 6 weeks after each of the subsequent IS. For the statistical analysis we used repeated measures ANOVA with IS as the within-subject factor. In order to test whether sphericity was violated a Mauchly-Test was carried out. Where the Mauchly-Test was found to be significant, we used a Greenhouse-Geisser correction.

In addition to the ANOVA analysis, pre- and post-treatment values of the data collected (diary data, SF-36, MSQ, HIT-6, BDI) were compared. For this purpose we computed the average of all post-treatment time points of the observation period (IS 1, IS 2, IS 3, IS 4) and compared the result with the value taken before the first BT-treatment. To this end a two-sided *t* test was carried out. We also present average absolute improvements (IMP) and average proportional improvements in percentage points (IMP %; only for parameters satisfying ratio scale properties). Finally, we report for all efficacy parameters Cohen's *d*, which expresses the size of an improvement in terms of its standard deviation (Cohen 1992).

In order to classify the response to BT therapy we compared pre-treatment headache days to post-treatment headache days. Patients, who showed a reduction of >50 % were defined as responders, a reduction between 30 and 50 % were defined as partial responders and a reduction between 0 and 30 % were defined as non-responders.

Results

Patients 27 Patients (age 45.6 $\pm$ 10.8 years, 25 females, 2 males, CM duration 27.5 $\pm$ 12.1 years) were enrolled in this study. 22 of the patients received all four IS of the observation period and continued therapy throughout the extension period. One patient dropped out after the second

IS because of continued therapy failure, one due to headache improvement after the first IS, one due to relocation after first IS, one due to attempted pregnancy after third IS. One patient was excluded from the study after the third IS due to failure to complete the questionnaires.

At study entry, 50 % of the patients received additional prophylactic medication (26.9 % amitriptyline, 7.7 % beta blocker, 3.8 % topiramate, 3.8 % pregabaline, 7.6 % multiple prophylactic drugs). Medication overuse was detected in 61.0 % of the patients (47.8 % with triptane on more than 10 days per month, in 8.7 % with non-steroidal anti-inflammatory drugs on more than 15 days per month, 4.3 % with a combination overuse).

BT therapy Altogether 176 IS were recorded, 100 in the observation period, 76 in the extension period. During the observation and the extension period altogether 6.5 ± 2.9 (minimum 4, maximum 13) IS were applied per patients equaling a total treatment time of 73.1 ± 36.9 weeks. The BT dose was 189.7 ± 45.8 MU. The therapeutic BT effect started after 5.5 ± 4.1 days and lasted for 10.4 ± 2.0 weeks. In 23 of 176 treatment cycles (13.1 %) adverse effects were reported. In 5.7 % neck muscle weakness occurred, in 3.4 % myalgia, in 2.3 % headache (migraine attack within 1 day after BT injection), in 1.1 % ptosis and in 0.6 % haematoma. All of the reported adverse effects were transient and did not lead to abandonment of therapy.

Efficacy 26 out of the 27 patients (96.3 %) reported a therapeutic effect. According to our responder definition 17 patients (63.0 %) were responders, 7 patients (25.9 %) partial responders and 3 patients (11.1 %) non-responders.

As shown in Table 1 headache days were significantly reduced from 18.9 ± 3.9 to 8.7 ± 4.5 ($p < 0.001$; −53.7 %), migraine days from 16.8 ± 4.9 to 7.4 ± 4.6 ($p < 0.001$; −55.1 %), autonomic days from 8.6 ± 7.5 to 2.7 ± 4.2 ($p < 0.001$; −71.9 %) and medication days from 14.2 ± 4.6 to 8.3 ± 4.2 ($p < 0.001$; −40.3 %) throughout the observation period. Figure 1 shows stability of the improvement throughout the observation period.

Table 2 shows significant improvement of all SF-36 items by 0.6–1.5 standard deviations, of all MSQ items by 1.4–2 standard deviations, of HIT-6 by 1.9 standard deviations and of BDI by 1.1 standard deviations. GCI was 2.6 ± 0.6. Again, all improvements were stable throughout the observation period.

Discussion

Patients In our prospective study we studied 27 CM patients who underwent BT therapy in a real-life situation. Our study cohort was representative for CM patients. Female predominance and mean age between 40 and 50 years have been found in previous sociodemographic (Blumenfeld et al. 2011; Buse et al. 2010) and interventional studies (Aurora et al. 2011; Cernuda-Morollon et al. 2014; Conway et al. 2005; Diener et al. 2007; Freitag et al. 2008; Silberstein et al. 2000). Also the high prevalence of medication overuse is in line with other studies (Cernuda-Morollon et al. 2014; Diener et al. 2010; Khalil et al. 2014). Although concomitant depression is common in CM patients (Buse et al. 2010; Cernuda-Morollon et al. 2014), mean BDI before treatment is twice as high in our patients as in previously reported patients with chronic daily headache (Dodick et al. 2005) or CM (Diener et al. 2007).

Efficacy In our study occurrence of headache days, migraine days and medication days prior to treatment are similar to the occurrence described in the PREEMPT study (Aurora et al. 2011), but range below the rates of earlier studies in patients with CM or medication overuse headache (Conway et al. 2005; Dodick et al. 2005; Magalhães et al. 2010; Sandrini et al. 2011). Our data show considerable and highly significant improvements of 40.3–71.9 % in headache days, migraine days and medication days in 96.3 % of our patients. All of these effects are stable throughout the entire study period. Whilst no data has been published so far on BT-induced improvement of autonomic symptoms in CM, our data show considerable and highly significant improvement also on autonomic days. It remains unclear, whether this effect is caused indirectly by reduction of migraine days or by additional direct effects.

BT's therapeutic effects have a considerable and highly significant impact on the patient's quality of life, which was initially highly impaired. Quality of life improvement was documented by improvements of the all SF-36 items by 0.6–1.5 standard deviations, improvements of all MSQ items by 1.4–2 standard deviations, by improvement of HIT-6 by 1.9 standard deviations and by improvement of BDI by 1.1 standard deviations. Effects documented in our study are comparable with findings in previous studies on HIT-6 (Aurora et al. 2011; Cady et al. 2011; Khalil et al. 2014), SF-36 (Guitera et al. 2002) and MSQ (Aurora et al. 2011; Blumenfeld et al. 2010). Improvement of BDI might theoretically also be caused by additional antidepressive action of BT (Finzi and Rosenthal 2014; Magid et al. 2014; Wollmer et al. 2012). Global clinical improvement was 2.7 ± 0.6 on the GCI scale indicating a high degree of patient satisfaction.

BT therapy Latency and duration of BT's therapeutic effect in our patients are similar to those observed in BT therapy of cervical dystonia, hemifacial spasm or blepharospasm (Dressler et al. 2014; Kollewe et al. 2010, 2015; Mohammadi et al. 2009). In our study mean duration of effect was reported with 10.4 ± 2.1 weeks. These findings suggest

Table 1 Occurrence of headache, migraine and frequency of medication intake as documented by the migraine diary 4 weeks before initiation of BT therapy

	Pre-BT	IS 1	IS 2	IS 3	IS 4	All	*p* value (ANOVA)	*p* value (*t* test)	IMP	IMP %	Cohen's *d*
Headache days	18.9 ± 3.9	9.2 ± 6.2	7.5 ± 3.7	9.1 ± 5.9	9.0 ± 6.3	8.7 ± 4.5	<0.001	<0.001	10.2 ± 5.1	53.7 ± 21.1	2.0
Migraine days	16.8 ± 4.9	7.3 ± 5.9	6.0 ± 3.7	8.1 ± 6.4	8.1 ± 6.8	7.4 ± 4.6	<0.001	<0.001	9.4 ± 5.8	55.1 ± 22.9	1.6
Autonomic days	8.6 ± 7.5	2.6 ± 3.1	2.5 ± 3.0	2.8 ± 6.2	3.0 ± 6.3	2.7 ± 4.2	<0.001	<0.001	5.9 ± 6.4	71.9 ± 23.2	0.9
Medication days	14.2 ± 4.6	8.3 ± 4.4	7.1 ± 3.7	8.9 ± 5.7	8.8 ± 6.4	8.3 ± 4.2	<0.001	<0.001	5.9 ± 6.2	40.3 ± 25.8	1.0

p values (ANOVA analysis) indicated for the within-subject comparison and for the pre/post comparison (*t* test). IMP gives the therapy induced improvement of each parameter

Pre-BT 4 weeks before initiation of botulinum toxin therapy, *IS* injection series, *All* mean of IS 1 to IS 4, *IMP* improvement from Pre-BT to All, *IMP %* improvement from Pre-BT to All in percentage points, *Cohen's d* improvement in standard deviations

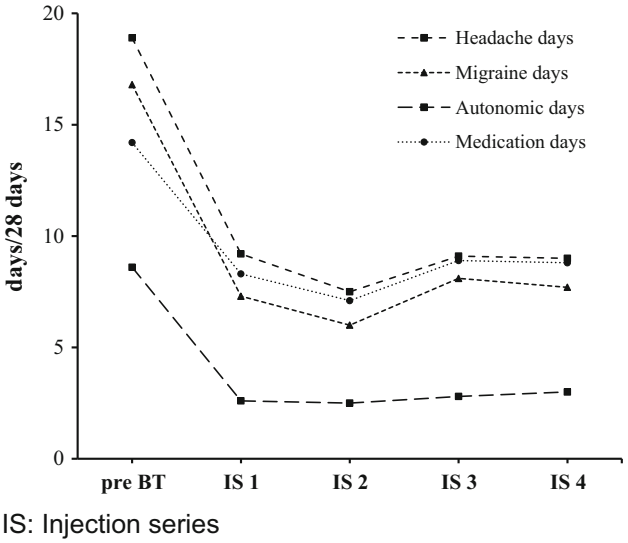

Fig. 1 Development of the migraine diary outcome parameters during the observation period. Outcome parameters were measured 4 weeks before initiation of BT therapy and in the interval of week 4–8 after each injection series

that a routine of 12 weeks between each treatment might be to long for a subgroup of patients. We propose that treatment intervals should be adapted individually for each patient.

Adverse effects rates in our study including muscular weakness, myalgia, ptosis, headache and hematoma are similar to those seen in other BT migraine studies (Aurora et al. 2014; Cernuda-Morollon et al. 2014; Sandrini et al. 2011). There was no indication of systemic adverse effects and no indication of BT antibody formation annihilating BT's therapeutic mode of action.

The mechanism of action of onabotulinumtoxinA in CM is still not fully understood. Numerous interactions between BT and pain transduction, transmission, perception and modulation are discussed (Matak and Lackovic 2014). In addition to the well-studied muscle relaxant effect BT can modulate the excretion of various neurotransmitters involved in pain pathways including substance P, calcitonin gene-related peptide (CGRP) and glutamate (Cui et al. 2004; Durham et al. 2004; Welch et al. 2000). OnabotulinumtoxinA is believed to reduce peripheral sensitization thus leading to a decrease of central sensitization (Aoki 2003).

In summary, our study confirms robust efficacy of onabotulinumtoxinA on primary symptoms of CM and their impact on quality of life in a very high percentage of patients treated. Adverse effects are minor and transient. Long-term data provided by this study demonstrate that these effects are continuous and stable and that no long-term adverse effects occur. Blinded studies and further animal studies are necessary to understand the underlying analgesic mechanisms.

Table 2 Study outcome parameters throughout the observation period

	Pre-BT	IS 1	IS 2	IS 3	IS 4	All	*p*-value (ANOVA)	*p* value (*t* test)	IMP	Cohen's *d*
Short form health survey (SF-36)										
Physical functioning	61.1 ± 29.6	82.7 ± 20.9	88.0 ± 10.9	83.0 ± 20.6	85.0 ± 16.3	84.6. ± 13.7	<0.001	<0.001	23.5 ± 26.9	0.9
Physical role functioning	21.6 ± 33.9	58.0 ± 41.1	47.7 ± 40.8	65.9 ± 38.2	56.9 ± 38.7	57.1 ± 33.9	<0.001	<0.001	35.6 ± 37.2	1.0
Bodily pain	16.1 ± 11.3	48.5 ± 21.2	46.8 ± 19.8	48.1 ± 18.4	48.0 ± 18.2	47.9 ± 15.0	<0.001	<0.001	31.7 ± 20.5	1.5
General health perceptions	36.9 ± 17.8	50.1 ± 17.9	50.5 ± 18.7	54.3 ± 20.1	51.3 ± 19.2	51.5 ± 16.3	<0.001	<0.001	14.6 ± 15.9	0.9
Vitality	32.5 ± 18.3	53.0 ± 18.4	49.1 ± 18.0	52.3 ± 19.2	52.0 ± 20.7	51.6 ± 16.9	<0.001	<0.001	19.1 ± 19.3	1.0
Social role functioning	36.4 ± 24.7	68.2 ± 25.5	65.3 ± 23.8	69.3 ± 24.6	66.5 ± 25.4	67.3 ± 19.4	<0.001	<0.001	31.0 ± 24.9	1.2
Emotion. role functioning	47.0 ± 45.6	69.7 ± 43.5	69.7 ± 38.4	77.3 ± 33.2	74.2 ± 41.1	72.7 ± 28.7	0.050	0.016	25.8 ± 46.4	0.6
Mental health	46.5 ± 19.7	66.9 ± 21.1	62.4 ± 18.2	67.4 ± 17.9	65.5 ± 22.8	65.5 ± 18.5	<0.001	<0.001	19.1 ± 20.9	0.9
Migraine-Specific Quality of Life Questionnaire (MSQ)										
Role function restrictive	29.5 ± 17.2	60.7 ± 23.8	62.8 ± 17.8	67.0 ± 18.8	65.6 ± 18.9	64.0 ± 12.2	<0.001	<0.001	34.5 ± 17.3	2
Role function preventive	44.0 ± 20.9	73.4 ± 18.5	71.4 ± 20.1	72.7 ± 19.1	73.9 ± 16.1	72.8 ± 12.0	<0.001	<0.001	31.3 ± 20.1	1.4
Emotional function	35.5 ± 23.8	74.5 ± 21.2	70.9 ± 20.6	76.7 ± 24.3	78.2 ± 20.7	75.1 ± 13.8	<0.001	<0.001	39.6 ± 24.1	1.6
Headache Impact Test (HIT-6)										
	68.7 ± 3.8	55.8 ± 7.8	60.0 ± 7.2	58.5 ± 4.6	58.9 ± 7.1	58.3 ± 5.1	<0.001	<0.001	10.4 ± 5.6	1.9
Beck Depression Inventory (BDI)										
	18.5 ± 11.6	10.1 ± 7.7	8.9 ± 6.4	9.5 ± 10.3	9.3 ± 11.2	9.5 ± 7.5	<0.001	<0.001	9.0 ± 7.9	1.1
Global Clinical Improvement (GCI)										
	n/a	2.6 ± 0.7	2.8 ± 0.5	2.7 ± 0.6	2.6 ± 0.6	2.6 ± 0.6	n/a	n/a	n/a	n/a

Assessments were performed 4 weeks before therapy initiation and 6 weeks after each injection series. *p* values (ANOVA analysis) indicated for the within-subject comparison and for the pre/post comparison (*t* test)

Pre-BT four weeks before initiation of botulinum toxin therapy, *IS* injection series, *All* mean of IS 1 to IS 4, *IMP* improvement from Pre-BT to All. SF-36; *MSQ* scores from 0 to 100, respectively, higher scores reflect better health-related quality of life, *HIT-6* scores from 36 to 78, lower scores indicate a lower degree of headache severity, BDI: ≤ 13: no/minimal depression, 14-19: depression mild depression, 20–28: moderate depression, ≥29: and severe depression. *Cohen's d* improvement in standard deviations, *n/a* not applicable

Compliance with ethical standards

Conflict of interest KK and BM received travel grants and honoraria for lectures from Allergan, Ipsen and Merz. LP received travel grants from Ipsen and Merz. MK received honoraria for lectures from Allergan. DD received honoraria for consultations from Allergan, Bayer, Eisai, IAB- Interdisciplinary Working Group for Movement Disorders, Ipsen, Merz, Syntaxin and UCB. He is shareholder of Allergan and holds several patents on Botulinum Toxins. CE, DUW and DF state that they have no conflict of interest.

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